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Published Fall 2000

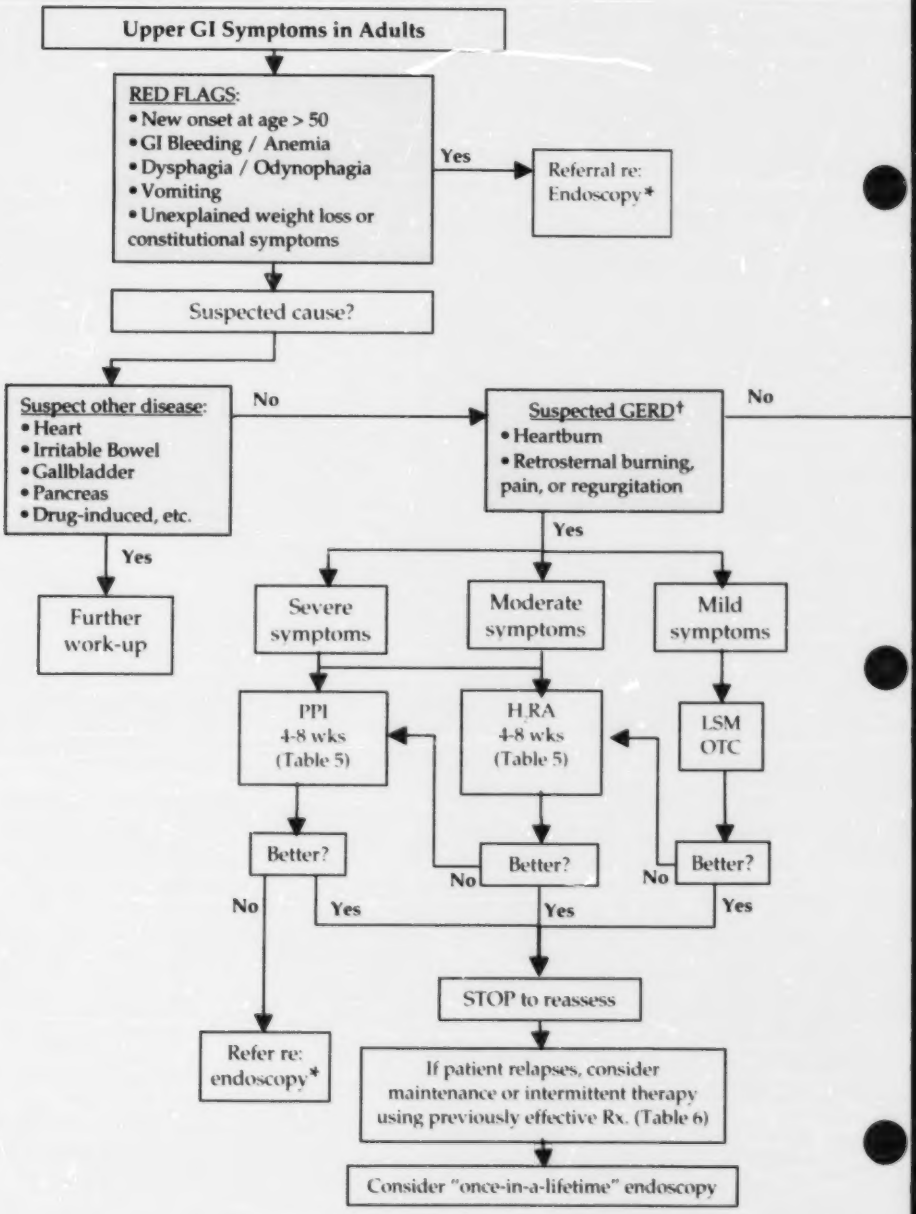
1st Edition

Ontario Guidelines for Peptic Ulcer Disease and Gastroesophageal Reflux

Ontario Program for Optimal Therapeutics

Guide to the Guidelines

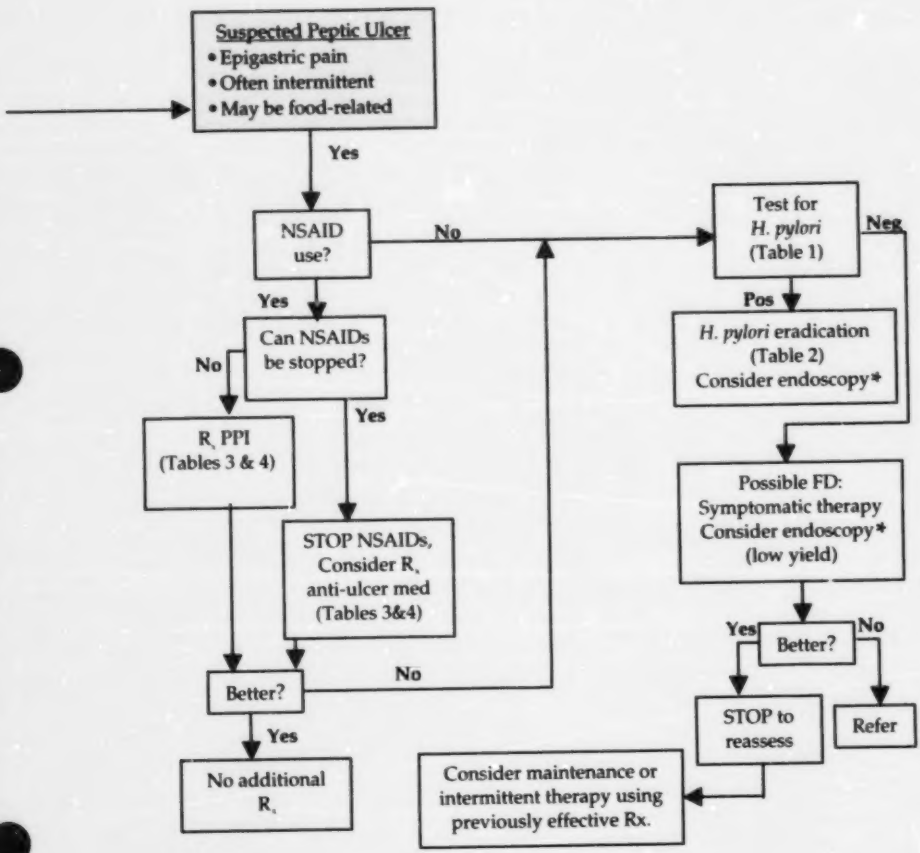
Figure 1: Diagnostic and Management Algorithm



* Endoscopy is more sensitive and specific then barium studies. For DU, barium studies have sensitivity of 50-63% and specificity of 97-100%; for GU, sensitivity is 22-91% and specificity is 97-100%.[5,6,7]

† Gastroesophageal reflux may present as chest pain, hoarseness, chronic cough, asthma and dysphagia. Rule out cardiac causes before proceeding with algorithm

GERD = gastroesophageal reflux disease; DU = duodenal ulcer; GI = gastrointestinal; GU = Gastric ulcer; H_2RA = H_2 receptor antagonist; LSM = lifestyle modifications; OTC = over-the-counter medications; PPI = proton pump inhibitor; R_x = therapy with



* Endoscopy is more sensitive and specific then barium studies. For DU, barium studies have sensitivity of 50-63% and specificity of 97-100%; for GU, sensitivity is 22-91% and specificity is 97-100%.[5,36,37]

FD = Functional dyspepsia (non-ulcer dyspepsia) – no objective cause for symptoms; GI = gastrointestinal; Neg = negative; NSAID = non-steroidal anti-inflammatory drugs; OTC = over- the-counter medications; Pos = positive; PPI – Proton pump inhibitor; R_x = therapy with

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ISBN 1-894706-01-3

Citation: Holbrook AM (Chair) for Ontario GI Therapy Review Panel. Ontario Guidelines for Peptic Ulcer Disease and Gastroesophageal Reflux. Toronto. First Edition. Queen's Printer of Ontario, 2000.

Acknowledgment: Support for the development, production and distribution of this guideline was provided by the Ontario Program for Optimal Therapeutics (OPOT), made possible through a grant from the Ontario Ministry of Health and Long-Term Care.

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This publication is based on information from sources believed to be reliable. While great effort has been taken to assure the completeness and accuracy of the information, it is not intended to reprint all of the information available on the subject of the publication, but rather to compile, complement and supplement other available sources. The Review Panel, publisher, printer and others contributing to the preparation of this document cannot accept liability for errors, omissions or any consequences arising from the use of the information.

Inclusion of a pharmaceutical product in these guidelines was determined solely on the basis of the Review Panel's expert professional assessment of the available evidence. It is not intended, and cannot be taken, as a recommendation that the product be included in the reimbursement policies of any drug plan or benefits manager.

Stakeholder groups were invited to participate in the development of these guidelines by reviewing and commenting upon the guidelines in draft form. These included health care professionals, professional societies, the pharmaceutical industry and the Ontario Ministry of Health and Long-Term Care.

Comments: A form is provided at the end of the document for the submission of reader's suggestions.

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Ontario Guidelines For Peptic Ulcer Disease and Gastroesophageal Reflux

Ontario GI Therapy Review Panel

June, 2000

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In addition, a draft of this guideline was submitted to many other clinicians for their consideration.

Section I

Introduction

SECTION I: INTRODUCTION

1.1 Purpose and Organization of Guideline

This guideline was commissioned and funded by the Ontario Program for Optimal Therapeutics (OPOT). OPOT is an independent agency established with a grant from the Ontario Ministry of Health and Long-Term Care (MOHLTC). The Ministry participated in the guideline development only as one of the stakeholder groups asked to review and comment upon the guideline in draft form (along with health care professionals, professional societies, the pharmaceutical industry and others). OPOT's mandate is to provide Ontario health professionals with evidence-based recommendations for the cost-effective treatment of various conditions. A second component of OPOT's mandate is to develop methods of incorporating these guidelines into practice.

The recommendations provided herein focus on therapy for two important causes of upper GI symptoms for which good quality evidence exists, namely peptic ulcer disease (PUD) and gastroesophageal reflux disease (GERD). Although family physicians often see patients with GI symptoms before definitive diagnoses are made, few studies are based on symptoms alone. A symptom/sign-based management algorithm (Figure 1) was derived from various published sources[1-4] and modified where additional evidence was identified.[4,5] Guideline users are referred to other sources[2,3,6,7] for further elaboration on the diagnosis of patients based on symptoms, signs and laboratory tests.

These guidelines were developed using rigorous methods, including a thorough literature search for relevant trials, meta-analyses, practice guidelines, and economic analyses, and critical appraisal of more than 1700 papers.[7-9] In some cases, systematic overviews or meta-analyses[10] were carried out to clarify which agents should be first-line or alternate. Costs to the provincial health care plan were considered. A grade has been assigned to each recommendation indicating the strength of its supporting evidence (Section 1.3). Tables are provided which summarize the recommended therapies including citation of high quality studies. Drugs are classified as first-line or alternative therapies. Drugs or regimens are designated "first-line" based on strength of efficacy data, adverse effect profile, cost, availability, and convenience. Although head-to-head studies comparing the different proton pump inhibitors (PPI) or histamine-2-receptor antagonists (H_2RA) are lacking, healing rates and symptom relief are comparable within each class.[7,9,11-26] Therefore, within the first-line and alternative designations, drugs or regimens are listed in alphabetical order by class. For the H_2RAs, generic cimetidine is the least expensive; pantoprazole is the least expensive PPI (see notes in charts).

All costs were calculated using the Ontario Drug Benefit (ODB) formulary costs for the lowest priced interchangeable product. In cases where no ODB data are available costs were obtained from the manufacturer. Professional fees and markups were not included in the costs listed in the tables since they vary by consumer and geographical area.

Once the draft document was developed, a review panel was formed consisting of family physicians, gastroenterologists, clinical pharmacologists, pharmacists, and epidemiologists representing each region of the province, academic and community practice, as well as clinicians and researchers (Appendix A). This group reviewed and edited the first draft of the current document. Suggestions for revisions supported by evidence were incorporated into the second draft, which was then reviewed by a larger consensus panel. As a result of these deliberations, a third draft was formulated for circulation to members of both panels as well as external stakeholders including all relevant professional societies, government branches, pharmaceutical companies, consumers plus additional experts and providers. Modifications and updates were again reviewed by panelists and stakeholders and a final draft formulated for publication. As with any consensus process, the degree of endorsement of each recommendation by individual panelists varies.

1.2 Use of Guidelines

These guidelines are intended to assist clinicians, especially family physicians, in caring for adults with PUD and GERD. PUD and GERD are important causes of dyspepsia but many cases of dyspepsia represent non-ulcer or functional dyspepsia for which only symptomatic therapy is recommended.[27-29]. They do not provide advice for children or pregnant women, for ulcers of rare etiology such as Zollinger-Ellison syndrome, or for complications of PUD such as hemorrhage. Guideline users are encouraged to seek specialist opinion if malignancy or other unusual and dangerous etiologies are suspected (e.g., therapeutic failures, presentation with alarm signs and symptoms such as unexplained weight loss, anorexia, hemorrhage, anemia, persistent vomiting, dysphagia, or odynophagia).

1.3 Levels of Evidence and Strength of Recommendations

The following grades were used to indicate the level of evidence supporting each recommendation:[30,31]

Grade A[‡]**:**	Best evidence from well designed, randomized controlled trials (RCT) or meta-analyses adequately powered to show a clinically important result.
Grade B[•]**:**	Best evidence from well designed RCTs or meta-analyses in which a clinically important result is likely but not definite.
Grade C:	Best evidence from non-randomized trials, concurrent cohort studies.
Grade D:	Best evidence from before-after studies, case series, expert opinion, or consensus.

[‡] Grade A is further defined as RCTs or meta-analyses in which there is no heterogeneity of results studied and the 95% confidence interval for the treatment effect exceeds the minimal clinically important effect.

[•] Grade B is further defined as RCTs or meta-analyses in which there is heterogeneity among the results studied or the 95% confidence interval for the treatment effect overlaps the minimal clinically important effect.

Section II

Managing Patients with Upper Gastrointestinal (GI) Complaints

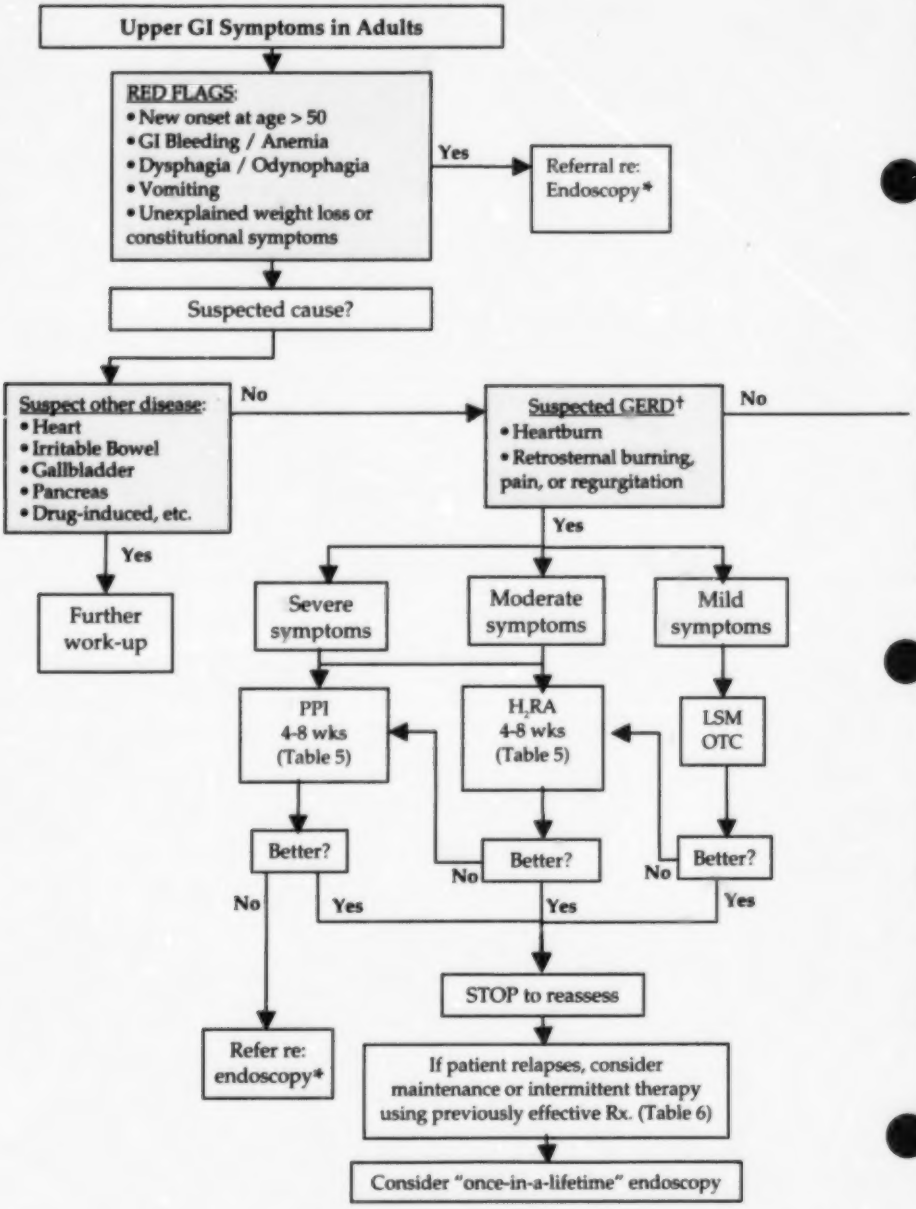
SECTION II: MANAGING PATIENTS WITH UPPER GASTROINTESTINAL (GI) COMPLAINTS

2.1 Overview

Upper gastrointestinal (GI) complaints are extremely common. In recent surveys of Canadian adults, 38-40% of individuals suffered from upper GI complaints including heartburn, acid indigestion, abdominal discomfort or distention, and dyspepsia.[32,33] Thirty-four percent had used some drug treatment within the previous six months for relief of these conditions.[32] The treatment of these complaints currently costs the Ontario Ministry of Health and Long-Term Care more than $120 million per year.

The algorithm shown in Figure 1 outlines an approach to the assessment of patients presenting with upper GI symptoms. Its origins are discussed in Section 1.1. For the purposes of these guidelines, the definition of **dyspepsia** is upper abdominal pain or discomfort.[27,34,35] The treatment of **functional dyspepsia** (symptoms without ulcer on endoscopy) is not addressed in these guidelines but readers can consult a recent review for details regarding this condition.[27] Although the management algorithm is based on high quality diagnostic and therapeutic evidence, different management strategies have not themselves been tested in RCTs.[1]

Figure 1: Diagnostic and Management Algorithm

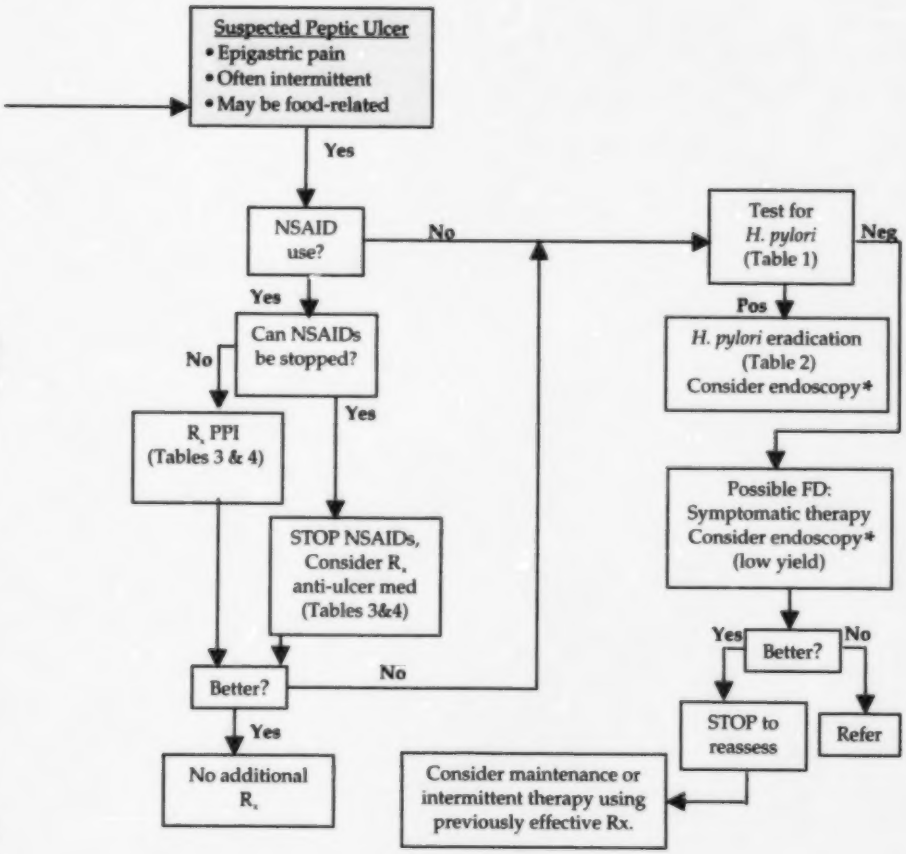


* Endoscopy is more sensitive and specific then barium studies. For DU, barium studies have sensitivity of 50-63% and specificity of 97-100%; for GU, sensitivity is 22-91% and specificity is 97-100%.[5,36,37]

†Gastroesophageal reflux may present as chest pain, hoarseness, chronic cough, asthma and dysphagia. Rule out cardiac causes before proceeding with algorithm

GERD = gastroesophageal reflux disease; DU = duodenal ulcer; GI = gastrointestinal; GU = Gastric ulcer; H_2RA = H_2 receptor antagonist; LSM = lifestyle modifications; OTC = over-the-counter medications; PPI = proton pump inhibitor; R_x = therapy with

Figure 1: Diagnostic and Management Algorithm (cont'd)



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FD = Functional dyspepsia (non-ulcer dyspepsia) – no objective cause for symptoms; GI = gastrointestinal; Neg = negative; NSAID = non-steroidal anti-inflammatory drugs; OTC = over- the-counter medications; Pos = positive; PPI – Proton pump inhibitor; Rx = therapy with

Section III

Peptic Ulcer Disease (PUD)

SECTION III: PEPTIC ULCER DISEASE (PUD)

3.1 Overview

PUD comprises ulceration of either the gastric or duodenal mucosa and has a lifetime incidence of approximately 10% for men and 4% for women.[38] Classic ulcer-like dyspepsia has been defined as a distinct, localized epigastric pain that is often intermittent, may be persistent and is often relieved by eating. There is a poor correlation between dyspeptic symptoms and the presence of ulcers.[39] It was long held that stress, diet and excess gastric acid were the causes of most cases of chronic PUD. However, the discovery that *Helicobacter pylori (H. pylori)* infection is a major factor in the development of PUD has revolutionized the understanding of its pathogenesis.[40,41] Most patients (>90%) with duodenal ulcers (DU) and the majority of patients (70-84%) with gastric ulcers (GU) are infected with *H. pylori*.[5,7,42-44] Because eradication therapy is becoming more common, the relative proportion of non-*H. pylori* associated PUD is increasing.[45] Only a small proportion (15-20%) of those infected with *H. pylori* develop ulceration.[43,44] The strongest evidence linking *H. pylori* causally with peptic ulcers is the dramatic reduction in recurrence rates from >60% per year with intermittent acid suppression therapy to <5% per year after *H. pylori* eradication.[46,47]

Non-steroidal anti-inflammatory drugs (NSAIDs) are the second most common cause of ulcers.[48,49] The prevalence of endoscopically proven GUs ranges from 0.3% in the general population to 12-30% in arthritics who have taken NSAIDs over months. In the same arthritic patients, the prevalence of DU is estimated to range from 2-19% as compared to 1.4% in the general population.[50-52]

Cigarette smoking is a risk factor for PUD and has been shown to decrease the benefit of anti-secretory therapy.[53-56] The various other etiological factors (e.g., benign and malignant tumors) are much less common but need to be investigated when patients present with recurrent ulcers not related to *H. pylori* or NSAIDs.[48] The most common complication of PUD is bleeding which is associated with 15-20% of peptic ulcers.[57] Other less common complications include perforation (5%), and pyloric or occasionally duodenal obstruction.[38]

The shift in the understanding of the pathogenesis of PUD has generated a major change in PUD treatment. While acid suppression alone was the cornerstone of ulcer therapy in the 1980s, the discovery of *H. pylori* introduced the era of eradication therapy using antibiotics combined with acid suppression or bismuth-containing agents.

The focus of this section of the guidelines is on the therapy of PUD. Readers are referred to definitive review articles for details on the diagnosis of PUD.[27,58,58,59] In general, diagnostic tests for *H. pylori* should be performed only when the clinician plans to treat patients with positive results using eradication therapy. Non-endoscopic tests (i.e., carbon isotope urea breath tests and serology) are appropriate for patients under 50 years of age with a history of peptic ulcer or with chronic symptoms consistent with peptic ulcer provided that the patient has no alarm signs or symptoms. Although quantitative serologic titres are often reported, there is little evidence that these are useful in directing management. Endoscopy is recommended for symptomatic patients with alarm signs or symptoms, those with a history of NSAID use, or those who are older than 50 years of age. A summary of *H. pylori* diagnostic tests is provided in Table 1.

It may be appropriate to confirm *H. pylori* eradication in patients with GU or complicated DU using either endoscopy with biopsy or urea breath test.[7] A follow-up endoscopy to document healing is recommended for all patients with GU.[7] Serology remains positive for some time after eradication and thus is **not useful** to prove eradication.[7] In order to avoid false-negative results, confirmatory tests should be performed at least 4 weeks after completion of the eradication therapy and *at least* 7 days after stopping the proton-pump inhibitor (PPI) or histamine-2-receptor antagonist (H_2RA).[7,60-63]

*Table 1: H. pylori Diagnostic Tests**

Test	Sensitivity	Specificity	Relative Cost†	OHIP Coverage
ENDOSCOPIC TESTS				
Histology	95-99	95-99	$$$$$	Yes
Rapid Urease Test	90-95	95	$$$$$	Yes
Culture	80	90-100	$$$$$	Yes
NON-ENDOSCOPIC TESTS				
^{13}C Urea Breath Test	90-95	90-95	$	No
^{14}C Urea Breath Test	90-95	90-95	$	Yes
Blood serology (lab)	85-95	85-90	$	Yes
Blood serology (office)	85-90	85-90	$	No

* Adapted with permission from the Canadian Journal of Gastroenterology.[7]

† These values are estimates only. The cost of histology, the urease test and culture relate largely to the expense of the endoscopy, including the physician's fee and hospital costs including purchase of equipment and nursing costs;

$ Cost of test: $=Less than $100; $$=$100-200; $$$=$200-300; $$$$=$300-400; $$$$$=>$400

3.2 *PUD Bottom Line*

1. To optimize drug therapy and minimize the risk for recurrences, patients should be instructed on the general principles of peptic ulcer management and lifestyle modifications (e.g., stop NSAID use, stop smoking, and minimize the use of alcohol).
2. The major focus of PUD management in primary care should be *H. pylori* eradication in patients with confirmed infection.
3. *H. pylori* is most effectively eradicated using multiple drug therapy consisting of a PPI or RBC plus 2 antimicrobial agents (currently, clarithromycin plus either amoxicillin or metronidazole) for 7 days. Acid suppression therapy beyond the end of eradication therapy is generally not necessary to achieve ulcer healing.
4. Alternate regimens (bismuth subsalicylate, metronidazole, and tetracycline [BMT] with or without H_2RA) may be used if cost is an issue for the patient and compliance can be assured.
5. Regimens consisting of a PPI plus 1 antibiotic (e.g., clarithromycin or amoxicillin) are NOT recommended because they produce lower cure rates than the above regimens.
6. The management of NSAID-related PUD involves stopping NSAID therapy and treating the ulcer with standard acid suppression therapy.
7. An H_2RA is recommended when NSAID treatment is stopped and for uncomplicated NSAID-associated ulcer treatment because it is effective in this condition and has a lower cost compared with PPIs.
8. Routine testing and *H. pylori* eradication in NSAID-associated PUD has not been proven to be worthwhile.
9. Misoprostol, high-dose H_2RA, and PPIs are useful for prevention of serious gastric complications in NSAID users who cannot discontinue the NSAID and are identified as high risk for developing NSAID-related ulcers (i.e., >65 years old, history of ulcers or GI bleeding, and/or cardiovascular disease).
10. All H_2RAs have similar ulcer healing rates and side effect profiles but cimetidine has a higher potential for interaction with theophylline, phenytoin, and warfarin. Generic cimetidine is the least expensive and is therefore recommended where these drug interactions would not apply or where the therapies can be closely monitored.
11. PPIs (i.e., omeprazole, lansoprazole and pantoprazole) are all considered to be effective and safe. Pantoprazole is the least expensive.

3.3 *Treatment of* H. pylori – *Positive Peptic Ulcer Disease*

Compared with intermittent acid suppression, *H. pylori* eradication therapy facilitates ulcer healing and reduces ulcer recurrence rates several-fold.[46] *Helicobacter pylori* eradication consists of a combination of antibiotics plus an acid-suppressing agent for early symptomatic relief. After successful eradication therapy, recurrence rates are expected to be <5% annually.[46,47] The following recommendations for *H.pylori* eradication are based on recent meta-analyses, current treatment guidelines, and a cost-effectiveness analysis of RCTs.[7,64-69]

It is important to note that the 7 to14-day eradication regimens are all that is necessary in order to facilitate ulcer healing. Follow-up acid suppression therapy after eradication is not necessary[70-72] unless symptoms persist, the patient has had a serious complication (e.g., hemorrhage), or is at risk in the event of a complication because of comorbid illness.

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Table 2 – Regimens for H. pylori-Positive Peptic Ulcer Disease

Regimen	Evidence	Duration (days)	Eradication Rates[60]	Regimen Cost[§]	Comments
First Line Therapy					
PPI or RBC* plus C & M Lansoprazole 30mg bid OR Omeprazole 20mg bid OR Pantoprazole 40mg bid OR Ranitidine Bismuth Citrate* 400mg bid PLUS Clarithromycin 250mg bid AND Metronidazole 500mg bid	L[73,74] O[75-77] RBC[78-87] P[88-91]	7	78-83%	PPI Regimens $48.09-52.29 RBC Regimen $43.51-55.75	• *Regimens of choice because of high eradication rates, short duration, and low level of complexity.*[744] • *Efficacy is decreased by clarithromycin*[92] *or metronidazole resistance.*[93]
PPI or RBC* plus C & A Lansoprazole 30mg bid OR Omeprazole 20mg bid OR Pantoprazole 40mg bid OR Ranitidine Bismuth Citrate* 400mg bid PLUS Clarithromycin 500mg bid ANDAmoxicillin 1g bid	L[94] O[76,94-99] RBC[81-83,99-101] P[102,103]	7	80-81%	PPI Regimens $73.64-77.84 RBC Regimen $66.24	• *Lansoprazole, clarithromycin, amoxicillin available as combination package.* • *Efficacy decreased by clarithromycin*[92] *resistance.*
PPI plus A & M Lansoprazole 30mg bid OR Omeprazole 20mg bid OR Pantoprazole 40mg bid PLUS Amoxicillin 1g bid AND Metronidazole 500mg bid	L[74,95,104] O[74,85,95,105-110] P[No RCT]	7	79%	$33.01-37.21	• *Eradication rates may be lower than clarithromycin-containing regimens based on head-to-head comparisons.*[88,111,112] • *Efficacy decreased by metronidazole resistance.*[92,93,113]
H_2RA plus –B & M & T Cimetidine 400mg bid OR Famotidine 20mg bid OR Nizatidine 150mg bid OR Ranitidine 150mg bid PLUS Bismuth subsalicylate 2 tabs qid AND Metronidazole 500mg tid or 250mg qid AND Tetracycline 500mg tid or 250mg qid	C[No RCT] F[No RCT] N[No RCT] R[105,114,115]	14	80%	$20.17-35.39	• *Bismuth subsalicylate not covered by ODB.*
PPI plus –B & M & T Lansoprazole 30mg bid OR Omeprazole 20mg bid OR Pantoprazole 40mg bid PLUS BMT (doses as above)	L[No RCT] O[70,97,116-118] P[No RCT]	7	82%	$34.80-39.66	• *Bismuth subsalicylate not covered by ODB.*
Alternate Therapy					
B & M & T (doses as above)	[70,119-122]	14	75%	$16.39-17.71	• *Lower efficacy.* • *Reasonable alternative drug therapy at lower cost; regimen complexity and duration may impair compliance.*[123] • *Bismuth subsalicylate not covered by ODB.*

Notes:

- **Recurrences:** For *H. pylori* positive ulcer recurrences, an alternate regimen that does NOT include the same two antimicrobial agents should be selected and treatment should be extended to 14 days.[50,124] Urea breath tests or endoscopic tests, not serology, are recommended for diagnosis of recurrence.
- Antimicrobial **resistance** can occur with metronidazole and clarithromycin[125-132] and can significantly reduce eradication rates.[113,115,133,134]
- **Follow-up:** The recommended test to confirm *H. pylori* eradication is the urea breath test if follow-up is deemed necessary.[6,7] Follow-up testing should be performed at least 4 weeks after completing *H. pylori* therapy and at least 7 days after stopping PPI or H_2RA.[60,61] Follow-up endoscopy is essential for patients with ulcer complications (bleeding, perforation, stricture), GU, or refractory ulcers; repeat endoscopy with biopsy is recommended for complicated, giant or refractory ulcers.
- **Smoking:** has been associated with delayed healing and increased recurrences; cessation should be encouraged.[138]
- **Compliance** rates of <60-80% have been associated with reduced eradication rates.[136,137]
- **Adverse effects** such as pseudomembranous colitis and severe drug reactions occur rarely. Minor adverse effects occur in 30-50% of patients.[48]
- **PPI:** PPIs are all considered to be safe and effective. Pantoprazole is the least expensive.
- **Amoxicillin:** not to be substituted with ampicillin,[139] and may be taken with or without food.[139]
- **Clarithromycin:** not to be substituted with erythromycin,[140,141] taste disturbance common, drug interactions common .[139] Note dose differences between PPI-CM and PPI-CA.[142]
- **Metronidazole:** metallic taste; potential disulfiram-like reaction with concurrent alcohol.[139]
- **Bismuth:** diarrhea, taste disturbances, headache; avoid in renal failure (CrCl<30ml/min)

A = amoxicillin; B = Bismuth subsalicylate; C = clarithromycin; H_2RA = histamine-2 receptor antagonist; L = Lansoprazole; M = metronidazole; O = Omeprazole; P = Pantoprazole; PPI = proton pump inhibitor; RBC = Ranitidine Bismuth Citrate; RCT = Randomized Controlled Trial;
T = tetracycline.

* Ranitidine bismuth citrate 400mg tablets contain equivalent of 162mg ranitidine (base), 128mg of trivalent bismuth, and 110mg of citrate.

$ Approximate drug costs were derived from the ODB formulary or manufacturers and do not include professional fees or markups.

Eradication therapy for *H. pylori* –associated ulcers is highly recommended. All of the first-line regimens appear similar in efficacy.[7,69]

This is a grade A recommendation.

Treatment for *H. pylori* eradication failures is not well defined yet.

Table 2 – Regimens for H. pylori-Positive Peptic Ulcer Disease

Regimen	Evidence	Duration (days)	Eradication Rates[68]	Regimen Cost[$]	Comments
First Line Therapy					
PPI or RBC* plus C & M Lansoprazole 30mg bid OR Omeprazole 20mg bid OR Pantoprazole 40mg bid OR Ranitidine Bismuth Citrate* 400mg bid PLUS Clarithromycin 250mg bid AND Metronidazole 500mg bid	L[73,74] O[75–77] RBC[78,87] P[88,91]	7	78-83%	PPI Regimens $48.09-52.29 RBC Regimen $43.51-55.75	• *Regimens of choice because of high eradication rates, short duration, and low level of complexity.*[74] • *Efficacy is decreased by clarithromycin*[92] *or metronidazole resistance.*[93]
PPI or RBC* plus C & A Lansoprazole 30mg bid OR Omeprazole 20mg bid OR Pantoprazole 40mg bid OR Ranitidine Bismuth Citrate* 400mg bid PLUS Clarithromycin 500mg bid AND Amoxicillin 1g bid	L[94] O[76,94,95] RBC[83,84,96,101] P[102,103]	7	80-81%	PPI Regimens $73.64-77.84 RBC Regimen $66.24	• *Lansoprazole, clarithromycin, amoxicillin available as combination package.* • *Efficacy decreased by clarithromycin*[92] *resistance.*
PPI plus A & M Lansoprazole 30mg bid OR Omeprazole 20mg bid OR Pantoprazole 40mg bid PLUS Amoxicillin 1g bid AND Metronidazole 500mg bid	L[74,85,104] O[74,85,95,105,110] P[NoRCT]	7	79%	$33.01-37.21	• *Eradication rates may be lower than clarithromycin-containing regimens based on head-to-head comparisons.*[95,111,112] • *Efficacy decreased by metronidazole resistance.*[92,93,113]
H_2RA plus –B & M & T Cimetidine 400mg bid OR Famotidine 20mg bid OR Nizatidine 150mg bid OR Ranitidine 150mg bid PLUS Bismuth subsalicylate 2 tabs qid AND Metronidazole 500mg tid or 250mg qid AND Tetracycline 500mg tid or 250mg qid	C[NoRCT] F[NoRCT] N[NoRCT] R[95,114,115]	14	80%	$20.17-35.39	• *Bismuth subsalicylate not covered by ODB.*
PPI plus –B & M & T Lansoprazole 30mg bid OR Omeprazole 20mg bid OR Pantoprazole 40mg bid PLUS BMT (doses as above)	L[NoRCT] O[75,97,116,118] P[NoRCT]	7	82%	$34.80-39.66	• *Bismuth subsalicylate not covered by ODB.*
Alternate Therapy					
B & M & T (doses as above)	[70,119,122]	14	75%	$16.39-17.71	• *Lower efficacy.* • *Reasonable alternative drug therapy at lower cost; regimen complexity and duration may impair compliance.*[123] • *Bismuth subsalicylate not covered by ODB.*

Notes:

- **Recurrences:** For *H. pylori* positive ulcer recurrences, an alternate regimen that does NOT include the same two antimicrobial agents should be selected and treatment should be extended to 14 days.[56,124] Urea breath tests or endoscopic tests, not serology, are recommended for diagnosis of recurrence.
- Antimicrobial **resistance** can occur with metronidazole and clarithromycin[125-132] and can significantly reduce eradication rates.[113,115,133,134]
- **Follow-up:** The recommended test to confirm *H. pylori* eradication is the urea breath test if follow-up is deemed necessary.[6,7] Follow-up testing should be performed at least 4 weeks after completing *H. pylori* therapy and at least 7 days after stopping PPI or H_2RA.[60,61] Follow-up endoscopy is essential for patients with ulcer complications (bleeding, perforation, stricture), GU, or refractory ulcers; repeat endoscopy with biopsy is recommended for complicated, giant or refractory ulcers.
- **Smoking:** has been associated with delayed healing and increased recurrences; cessation should be encouraged.[135]
- **Compliance** rates of <60-80% have been associated with reduced eradication rates.[136,137]
- **Adverse effects** such as pseudomembranous colitis and severe drug reactions occur rarely. Minor adverse effects occur in 30-50% of patients.[64]
- **PPI:** PPIs are all considered to be safe and effective. Pantoprazole is the least expensive.
- **Amoxicillin:** not to be substituted with ampicillin,[138] and may be taken with or without food.[139]
- **Clarithromycin:** not to be substituted with erythromycin,[140,141] taste disturbance common, drug interactions common .[139] Note dose differences between PPI-CM and PPI-CA.[142]
- **Metronidazole:** metallic taste; potential disulfiram-like reaction with concurrent alcohol.[139]
- **Bismuth:** diarrhea, taste disturbances, headache; avoid in renal failure (CrCl<30ml/min)

A = amoxicillin; B = Bismuth subsalicylate; C = clarithromycin; H_2RA = histamine-2 receptor antagonist; L = Lansoprazole; M = metronidazole; O = Omeprazole; P = Pantoprazole; PPI = proton pump inhibitor; RBC = Ranitidine Bismuth Citrate; RCT = Randomized Controlled Trial;
T = tetracycline.

* Ranitidine bismuth citrate 400mg tablets contain equivalent of 162mg ranitidine (base), 128mg of trivalent bismuth, and 110mg of citrate.

$ Approximate drug costs were derived from the ODB formulary or manufacturers and do not include professional fees or markups.

Eradication therapy for *H. pylori* –associated ulcers is highly recommended. All of the first-line regimens appear similar in efficacy.[7,69]

This is a grade A recommendation.

Treatment for *H. pylori* eradication failures is not well defined yet.

3.4 Treatment of NSAID-Associated Peptic Ulcer Disease

In addition to treating an NSAID-associated ulcer and its symptoms, it is important that NSAID therapy be discontinued whenever possible. Acetaminophen is as effective as NSAIDs in the treatment of mild-to-moderate osteoarthritis and does not have ulcerogenic effects.[143-146]

Note that the presence of dyspepsia on NSAID therapy does not correlate with the presence of ulcers; similarly serious GI complications related to NSAID therapy are often not preceded by symptoms of dyspepsia. [59] The trials guiding therapy examine endoscopic ulcers, most of which are clinically silent.

Routine testing for and eradicating *H. pylori* in patients embarking on NSAID therapy or with NSAID-related PUD is not currently recommended.[7,41,59,147-150] One well-designed RCT demonstrated a reduction in NSAID-related ulcer occurrence over 8 weeks when *H. pylori* was eradicated from infected patients prior to receiving NSAIDs for musculoskeletal disorders.[151] However, three other RCTs suggest no reduction in dyspepsia or ulcer recurrences with *H. pylori* eradication.[150,152,153] Two found that the presence of *H. pylori* was a positive predictor of healing and maintenance of remission.[152,153]

While an initial study[154] suggests benefit of double-dose H_2RA in the prevention of NSAID-associated ulcer, the higher dose has not been studied for treatment of established ulceration.

Table 3 – Treatment of NSAID-Associated Peptic Ulcer Disease

Drug	Evidence	Regimen*	Drug Cost $	Comments
First Line Therapy				
PPI:				
Lansoprazole	[155]	30mg daily x 4 weeks	$56.00	• *Indicated for the treatment of complicated, slowly healing, large ulcers, or cases with >10 erosions in stomach or duodenum especially where NSAIDs must be continued.*[59,132,156] *More costly than H_2RAs.* • *Healing may be delayed by continuing NSAID therapy – therapy should continued for at least 8 weeks in such cases.*[152] • *75-80% healed at 8 weeks while NSAID was continued.*[152,153] • *No difference between omeprazole doses of 20 mg/d and 40 mg/d.*[152,153] • *Better tolerated than high dose misoprostol.*[153]
Omeprazole	[152,153,156]	20mg daily x 4 weeks	$61.60	
Pantoprazole	(No RCT)	40mg daily x 4 weeks	$53.20	
H_2RA:				
Cimetidine	[157]	400mg bid x 8 weeks	$15.12	• *Because of efficacy and low cost, H_2RAs are indicated for the treatment of uncomplicated ulcers when NSAIDs are discontinued.*[59] • *63% healed at 8 weeks while NSAID was continued.*[152]
Famotidine	[158]	20mg bid x 8 weeks	$70.73	
Nizatidine	(No RCT)	150mg bid x 8 weeks	$65.79	
Ranitidine	[152,159,160]	150mg bid x 8 weeks	$45.27	
Misoprostol	[153,161]	200 µg tid or qid x 4 weeks	$38.04-50.72	• *71% healed at 8 weeks while NSAID was continued.*[153,162]

Notes:

- Rate of healing is associated with ulcer diameter. Large ulcers may require longer duration of treatment than indicated above to ensure ulcer healing.[163]
- Heavy smoking and continuation of NSAID therapy delay healing with H_2RAs.[135,156,160]
- Benefit of eradicating *H. pylori* in this setting is unproven.[7,41,59,147-149,151]
- **H_2RAs:** H_2RAs are considered equally effective; cimetidine is the H_2RA of choice because of its low cost. If patient is taking theophylline, phenytoin, or warfarin along with cimetidine, monitor for toxicity of these agents (or consider using alternate H_2RA).
- **PPIs**: PPIs are all considered to be safe and effective. Pantoprazole is the least expensive.

RCT – Randomized Controlled Trial

$ Approximate drug costs were derived from the ODB formulary and do not include professional fees or markups.

* Duration of treatment based on assumption that NSAID is discontinued.

Anti-ulcer therapy can be recommended to heal NSAID-related ulcers preferably in combination with discontinuation of the NSAID.

This is a grade A recommendation.

Table 3 – Treatment of NSAID-Associated Peptic Ulcer Disease

Drug	Evidence	Regimen*	Drug Cost $	Comments
First Line Therapy				
PPI:				
Lansoprazole	[illegible]	30mg daily x 4 weeks	$56.00	• *Indicated for the treatment of complicated, slowly healing, large ulcers, or cases with >10 erosions in stomach or duodenum especially where NSAIDs must be continued.* [illegible] *More costly than H2RAs.* • *Healing may be delayed by continuing NSAID therapy – therapy should continued for at least 8 weeks in such cases.*[illegible] • *75-80% healed at 8 weeks while NSAID was continued.*[illegible] • *No difference between omeprazole doses of 20 mg/d and 40 mg/d.*[illegible] • *Better tolerated than high dose misoprostol.*[illegible]
Omeprazole	[illegible]	20mg daily x 4 weeks	$61.60	
Pantoprazole	[illegible]	40mg daily x 4 weeks	$53.20	
H_2RA:				
Cimetidine	[illegible]	400mg bid x 8 weeks	$15.12	• *Because of efficacy and low cost, H2RAs are indicated for the treatment of uncomplicated ulcers when NSAIDs are discontinued.*[illegible] • *63% healed at 8 weeks while NSAID was continued.*[illegible]
Famotidine	[illegible]	20mg bid x 8 weeks	$70.73	
Nizatidine	[illegible]	150mg bid x 8 weeks	$65.79	
Ranitidine	[illegible]	150mg bid x 8 weeks	$45.27	
Misoprostol	[illegible]	200 µg tid or qid x 4 weeks	$38.04-50.72	• *71% healed at 8 weeks while NSAID was continued.*[illegible]

Notes:

- Rate of healing is associated with ulcer diameter. Large ulcers may require longer duration of treatment than indicated above to ensure ulcer healing.[illegible]
- Heavy smoking and continuation of NSAID therapy delay healing with H2RAs.[illegible]
- Benefit of eradicating *H. pylori* in this setting is unproven.[illegible]
- **H_2RAs:** H2RAs are considered equally effective; cimetidine is the H2RA of choice because of its low cost. If patient is taking theophylline, phenytoin, or warfarin along with cimetidine, monitor for toxicity of these agents (or consider using alternate H2RA).
- **PPIs**: PPIs are all considered to be safe and effective. Pantoprazole is the least expensive.

RCT – Randomized Controlled Trial

$ Approximate drug costs were derived from the ODB formulary and do not include professional fees or markups.

* Duration of treatment based on assumption that NSAID is discontinued.

Anti-ulcer therapy can be recommended to heal NSAID-related ulcers preferably in combination with discontinuation of the NSAID.

This is a grade A recommendation.

3.5 Prevention of NSAID-Associated Peptic Ulcer Disease

If possible, NSAIDs should be avoided in patients thought to be at high risk of serious GI events. Factors that independently increase the risk for NSAID-related ulcers include:[164]

1. Previous GI bleeding
2. Previous peptic ulcer
3. Age >75 years
4. History of cardiovascular disease

Risk increases significantly for patients with 2 or more risk factors and preventive therapy should be considered in such cases. Having the single risk factor of age or cardiovascular disease alone does not appear to increase risk excessively and may not warrant prophylaxis.[164,165] For example, misoprostol prophylaxis for all adults >52 years with rheumatoid arthritis (RA) costs an estimated $95,000 per serious GI event avoided compared to $4100 if reserved for those older than 75 years with a history of previous PUD.[166] Patients receiving corticosteroids in addition to NSAIDs are not at increased risk compared to NSAIDs alone according to a large RCT.[164] Those receiving corticosteroids alone do not require ulcer prophylactic therapy.[167]

3.5.1. The Role for Selective COX-2 Inhibiting NSAIDs

Specific cyclo-oxygenase–2 (COX-2) inhibitor NSAIDs such as celecoxib and rofecoxib appear to have similar efficacy to older NSAIDs. Early trial results suggested a favourable impact on endoscopic GI events.[168,169] However, there is increasing evidence that most endoscopic ulcers are unimportant clinically and endoscopic ulcers are easier to prevent than clinically important GI events.[170-172] A recent meta-analysis of rofecoxib trials found a mildy lower (i.e., rates of 1.3% versus 1.8% for COX-2 versus traditional NSAIDs) risk of serious GI events.[172] Dyspepsia rates with the COX-2 NSAIDs are the same or slightly lower than older NSAIDs.[168,169,173] Because of their pricing at the higher end of NSAID prices, they are likely only to be cost-effective for patients at high risk of serious GI events as defined above. Comparisons of COX-2 inhibitors with regular NSAIDs combined with misoprostol or omeprazole are not yet available. Concerns regarding COX-2 NSAIDs delaying ulcer healing as well as causing renal and hepatic impairment remain unresolved.

Based on evidence of similar efficacy and early evidence of somewhat lower rates of serious GI events, selective COX-2 inhibiting NSAIDs can be considered for patients at high risk of serious GI events.

This is a grade B recommendation.

Table 4 – Prevention of NSAID-Associated Peptic Ulcer Disease

Drug	Evidence	Regimen	Drug Cost$ (4 weeks)	Comments
First Line Therapy				
Misoprostol	162,164,174,175	200µg tid	$38.04	• *Supported by large trial in NSAID users with rheumatoid arthritis.*[164] *TID dose based on trial demonstrating equal efficacy and better tolerability than QID dosing.*[162] *Protects against GU and other serious upper GI complications with continued NSAID therapy.*[162,164,174,176]
PPI:				
Lansoprazole	(No RCT)	30mg daily	$56.00	• *PPIs are an alternative to misoprostol – less relapse in secondary prevention, better tolerated, but higher cost.*[152,153,176,177]
Omeprazole	152,153,177,178	20mg daily	$61.00	
Pantoprazole	179	40mg daily	$53.20	
Alternate Therapy				
H_2RA:				
Cimetidine	(No RCT)	800mg bid	$14.17	• *One trial supports the use of high-dose famotidine*[154] *Regular dose appears less effective than PPI.*[152,176]
Famotidine	154	40mg bid	$63.67	
Nizatidine	(No RCT)	300mg bid	$59.61	
Ranitidine	152	300mg bid	$43.61	

Notes:

- **Misoprostol**: diarrhea (4% discontinuation rate)[162]; avoid in women of child-bearing potential who are not receiving adequate birth control, or in those who are pregnant.
- **PPIs:** PPIs are all considered to be safe and effective. Pantoprazole is the least expensive.
- **H_2RAs**: H_2RAs are considered equally effective; cimetidine is the H_2RA of choice because of its low cost. If patient is taking theophylline, phenytoin, or warfarin along with cimetidine, monitor for toxicity of these agents (or consider using alternate H_2RA). Only one study using high-dose famotidine supports the use of an H_2RA for prevention of NSAID-associated ulcers. Equivalent doses are listed for other H_2RAs.[152]

RCT – Randomized Controlled Trial, GU – Gastric Ulcer

$ Approximate drug costs were derived from the ODB formulary and do not include professional fees or markups.

Anti-ulcer therapy is recommended for prevention of NSAID-associated peptic ulcer in high-risk patients.

This is a grade A recommendation.

3.5 Prevention of NSAID-Associated Peptic Ulcer Disease

If possible, NSAIDs should be avoided in patients thought to be at high risk of serious GI events. Factors that independently increase the risk for NSAID-related ulcers include:[164]

1. Previous GI bleeding
2. Previous peptic ulcer
3. Age >75 years
4. History of cardiovascular disease

Risk increases significantly for patients with 2 or more risk factors and preventive therapy should be considered in such cases. Having the single risk factor of age or cardiovascular disease alone does not appear to increase risk excessively and may not warrant prophylaxis.[164,165] For example, misoprostol prophylaxis for all adults >52 years with rheumatoid arthritis (RA) costs an estimated $95,000 per serious GI event avoided compared to $4100 if reserved for those older than 75 years with a history of previous PUD.[166] Patients receiving corticosteroids in addition to NSAIDs are not at increased risk compared to NSAIDs alone according to a large RCT.[164] Those receiving corticosteroids alone do not require ulcer prophylactic therapy.[167]

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Based on evidence of similar efficacy and early evidence of somewhat lower rates of serious GI events, selective COX-2 inhibiting NSAIDs can be considered for patients at high risk of serious GI events.

This is a grade B recommendation.

Table 4 – Prevention of NSAID-Associated Peptic Ulcer Disease

Drug	Evidence	Regimen	Drug Cost$ (4 weeks)	Comments
First Line Therapy				
Misoprostol	[162,164,174,175]	200µg tid	$38.04	• *Supported by large trial in NSAID users with rheumatoid arthritis.* [194] *TID dose based on trial demonstrating equal efficacy and better tolerability than QID dosing.* [162] *Protects against GU and other serious upper GI complications with continued NSAID therapy.* [162,164,174,176]
PPI:				
Lansoprazole	[Non-RCT]	30mg daily	$56.00	• *PPIs are an alternative to misoprostol – less relapse in secondary prevention, better tolerated, but higher cost.* [152,153,176,177]
Omeprazole	[152,153,177,178]	20mg daily	$61.00	
Pantoprazole	[179]	40mg daily	$53.20	
Alternate Therapy				
H_2RA:				
Cimetidine	[Non-RCT]	800mg bid	$14.17	• *One trial supports the use of high-dose famotidine* [154] *Regular dose appears less effective than PPI.* [152,176]
Famotidine	[154]	40mg bid	$63.67	
Nizatidine	[Non-RCT]	300mg bid	$59.61	
Ranitidine	[152]	300mg bid	$43.61	

Notes:

- **Misoprostol**: diarrhea (4% discontinuation rate)[162]; avoid in women of child-bearing potential who are not receiving adequate birth control, or in those who are pregnant.
- **PPIs:** PPIs are all considered to be safe and effective. Pantoprazole is the least expensive.
- **H_2RAs**: H_2RAs are considered equally effective; cimetidine is the H_2RA of choice because of its low cost. If patient is taking theophylline, phenytoin, or warfarin along with cimetidine, monitor for toxicity of these agents (or consider using alternate H_2RA). Only one study using high-dose famotidine supports the use of an H_2RA for prevention of NSAID-associated ulcers. Equivalent doses are listed for other H_2RAs.[152]

RCT – Randomized Controlled Trial, GU – Gastric Ulcer
$ Approximate drug costs were derived from the ODB formulary and do not include professional fees or markups.

Anti-ulcer therapy is recommended for prevention of NSAID-associated peptic ulcer in high-risk patients.

This is a grade A recommendation.

3.6 Refractory Peptic Ulcer Management

The most common causes of refractory and recurrent ulcer disease are 1) *H. pylori* infection (untreated or treatment failure) and 2) unrecognized NSAID use.[7] Specific history of OTC use of aspirin or NSAIDs, including non-oral forms should be reviewed. If the above are ruled out, a search for other possible causes is necessary including poor treatment compliance, incomplete healing of large ulcers, and other conditions such as Zollinger-Ellison syndrome or cancer. Referral to a specialist is recommended at this point.

3.6.1. Treatment Options for Refractory H. pylori-positive PUD

When initial therapy fails and a repeat attempt at eradication is indicated, it has been recommended to use different antibiotics and to extend the re-treatment duration to 14 days.[7,59,92] After a patient has received a course of therapy, serology is no longer a useful diagnostic test because it will remain positive for some time after eradication. The presence of *H. pylori* must be established using the urea breath test or an endoscopic test.

Alternate *H. pylori* eradication therapies are recommended as above, but these are based on few clinical trials.

This is a grade D recommendation.

3.6.2. Treatment options for Non-H. pylori Related PUD

Reversible risk factors for PUD including NSAID use, smoking, and heavy alcohol use should be reduced or eliminated.[54-56] Standard anti-ulcer therapy is recommended. High-dose PPI therapy is superior to H_2RA therapy in healing refractory DUs.[180,181] It is not recommended to combine PPIs with other acid suppressants (e.g., H_2RAs). Concomitant use of H_2RAs may impair PPI efficacy.[48,182]

Standard anti-ulcer therapy is recommended. For ulcers refractory to H_2RAs, PPIs can be recommended.[180,181]

This is a grade A recommendation.

3.7 Follow-up of PUD Patients

Follow-up endoscopy is indicated for patients with GU or complicated DU, as are multiple biopsies if ulceration persists. Re-testing for *H. pylori* needs to be delayed until 4 or more weeks after discontinuation of eradication therapy and at least 7 days after stopping PPIs, or H_2RAs to minimize the chance of false negative results.[7,60,61,62] Follow-up for *H. pylori* should be done using endoscopic tests or urea-breath test. Serology should <u>not</u> be used as a follow-up test because antibody titres will remain positive even in the setting of *H. pylori* eradication.

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This is a grade D recommendation.

3.6.2. Treatment options for Non-H. pylori Related PUD

Reversible risk factors for PUD including NSAID use, smoking, and heavy alcohol use should be reduced or eliminated.[54,56] Standard anti-ulcer therapy is recommended. High-dose PPI therapy is superior to H_2RA therapy in healing refractory DUs.[180,181] It is not recommended to combine PPIs with other acid suppressants (e.g., H_2RAs). Concomitant use of H_2RAs may impair PPI efficacy.[48,182]

Standard anti-ulcer therapy is recommended. For ulcers refractory to H_2RAs, PPIs can be recommended.[180,181]

This is a grade A recommendation.

3.7 Follow-up of PUD Patients

Follow-up endoscopy is indicated for patients with GU or complicated DU, as are multiple biopsies if ulceration persists. Re-testing for *H. pylori* needs to be delayed until 4 or more weeks after discontinuation of eradication therapy and at least 7 days after stopping PPIs, or H_2RAs to minimize the chance of false negative results.[7,60,61,62] Follow-up for *H. pylori* should be done using endoscopic tests or urea-breath test. Serology should <u>not</u> be used as a follow-up test because antibody titres will remain positive even in the setting of *H. pylori* eradication.

Section IV

Gastroesophageal Reflux Disease (GERD)

SECTION IV: GASTROESOPHAGEAL REFLUX DISEASE (GERD)

4.1 Overview

Gastroesophageal reflux disease (GERD) is a clinical syndrome resulting from acid reflux from the stomach to the esophagus. In contrast to PUD, there is no causal association between *H. pylori* and GERD.[7] Heartburn (or pyrosis), the cardinal symptom of GERD, affects 10% of people daily[183] and up to 40% monthly.[184] Despite the high prevalence of symptoms, few of these patients have positive findings on endoscopy and there is poor correlation between symptoms and grade of esophagitis.[185] Persistent symptoms, however, do have a negative impact on quality of life.[186,187]

The classic presentation of GERD includes a history of postprandial retrosternal burning and regurgitation, which is aggravated by recumbency and bending, and transiently alleviated by antacids. Atypical presentations of GERD include chest pain, hoarseness, cough, asthma and dysphagia.[188]

The pathogenesis of GERD has been attributed to dysfunction of normal anti-reflux mechanisms involving the lower esophageal sphincter and diaphragmatic crura.[189] Risk factors for GERD are those that are thought to interfere with these anti-reflux mechanisms and include certain foods, cigarette smoking, obesity, recumbency after meals and a variety of medications as described below.[190,191] Various medical conditions can increase the potential for reflux including pregnancy, scleroderma, motility disorders and acid hypersecretory states such as the Zollinger-Ellison syndrome.[188] Hiatus hernia (HH) is not synonymous with GERD but may contribute to its pathophysiology.[192,193] In one study a HH was found in 63% of patients with esophagitis, while 58% of the patients with a HH had esophagitis.[194]

Esophageal complications associated with GERD include esophagitis, stricture, Barrett's esophagus, and esophageal adenocarcinoma. An estimated 2.5% to 24% of patients with esophagitis will have complications.[195,196] The prevalence of Barrett's esophagus in symptomatic patients with GERD undergoing upper endoscopy is approximately 7.4-10 cases per 1000.[197] Up to 10% of patients with Barrett's esophagus may progress to esophageal adenocarcinoma.[198] Recent data also indicate that the frequency, severity, and duration of GERD symptoms may be associated with esophageal adenocarcinoma, regardless of the presence of Barrett's esophagus.[199]

The diagnosis of GERD can be presumed by a careful history alone in those patients who present with classical symptoms.[9] Whether or not patients with GERD should be subjected to endoscopy (i.e., once-in-a-lifetime endoscopy) is controversial.[2] The Canadian Consensus Conference on the Treatment of GERD recommends investigations in patients who present with "alarm" signs or symptoms (shown as "Red Flags" in Figure 1) including atypical chest pain, dysphagia or gastrointestinal bleeding. Investigation is also recommended for those over 50 years of age with severe symptoms, and those failing a 4-8 week course of antisecretory therapy who have not been previously investigated.[5,9,200-202] Endoscopy, which allows for grading of esophagitis and for biopsy of suspicious lesions, is suggested as the first-line of investigation.[3,203] Twenty-four hour ambulatory pH monitoring is useful to diagnose GERD in patients who have atypical symptoms, in those who do not have pathological changes on endoscopy, and in those refractory to a PPI.[203] However, it is important to note that more than half of patients with typical heartburn have endoscopy-negative disease.[3] As for PUD, most trials are based on endoscopy findings (esophagitis in this case) rather than symptoms and the two correlate poorly.[2,3]

The conventional approach to GERD therapy involves a 3-step process.[190] Lifestyle modifications (LSM) (see discussion below) and OTC products (i.e., alginic acid, antacids, and low-dose H_2RA) are used as initial therapy (Phase I) for mild symptomatic disease.[9] Mild disease is defined as: (a) symptoms occurring less than 3 times per week; (b) symptoms present for less than 6 months; (c) symptoms not interfering with daily activities; (d) pain (heartburn) intensity in symptoms of the

order of 1-3 out of 10.[9] Those who have persistent or concerning symptoms would normally seek medical advice. Phase IIa consists of prescription medications; namely H_2RAs. If symptoms persist despite 4-8 weeks of optimal therapy, use of a PPI is recommended (Phase IIb). Phase III consists of anti-reflux surgery which may be indicated for resistant cases in eligible and willing individuals. A great deal of controversy exists over the relative cost-effectiveness of this conventional "step-up" approach versus the alternative "step-down" therapy, the latter advocating starting with a PPI.[2,3,204] Available pharmacoeconomic studies are conflicting and none provide a clear answer for the Canadian setting.[64,205-209]

The goals of therapy are to ameliorate symptoms of heartburn and to prevent ulceration of the distal esophagus to prevent complications. There are significant variations in symptom response rates, healing rates, and costs associated with the different therapies; however disease recurrence is common to all. The choice of both initial and maintenance drug therapy has been the focus of much debate, and this topic has been extensively reviewed.[9,210-213] These guidelines make recommendations for the initial management and maintenance drug therapy based on available efficacy and cost data.

4.2 GERD Bottom Line

1. *H.pylori* does not appear to play a causal role in GERD.
2. Therapy for most patients with mild symptoms consists of a stepped approach starting with LSM and OTC medications and progressing to prescription drugs if necessary. More severe cases may require surgery.
3. Lifestyle modifications (LSM) are an important adjunct to therapy at all phases and continuous re-enforcement is recommended despite the fact that there are limited good quality data to support this. (Section 4.3.1)
4. Medications that can potentially worsen GERD should be discontinued and substituted with other therapies if possible (Section 4.3.2).
5. OTC medications (i.e., antacids, alginic acid, and low-dose H_2RAs) provide some symptomatic relief but are less effective than prescription medications, and do not heal esophagitis when present.
6. H_2RAs are recommended as first-line prescription agents for 4-8 weeks in the initial phase II treatment of GERD in patients with mild-to-moderate symptoms.
7. Cisapride has not proven routinely effective for GERD in primary care settings. It is also contraindicated in a large number of patients due to potential cardiac toxicity and serious drug interactions and has been recently removed from the Canadian market. (See Notes section below Table 5).
8. PPIs are more effective than H_2RAs or cisapride. In the step-up approach they are reserved for patients who have moderate-to-severe or prolonged symptoms, those with documented erosive esophagitis or other GERD complications, or for second-line use after failure of H_2RAs.
9. Maintenance therapy using the drug that treated the acute episode effectively is appropriate for patients whose symptoms recur after the initial treatment course.
10. Full doses of H_2RAs and PPIs are generally necessary for maintenance therapy, although lower doses may be effective in some patients.

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4.3 Initial Therapy For GERD – Phase I

Phase I therapy of GERD includes lifestyle modifications and OTC medications.[9,214]

4.3.1. Lifestyle Modifications

Although lifestyle changes have been poorly studied, options include the following:[3,9,190,195,210]

- Elevating head of bed by 15-30 centimeters (6-12 inches) (i.e., NOT use of additional pillows) to reduce frequency of reflux episodes at night.[215,216]
- Losing weight if overweight.[217]
- Avoiding caffeine and alcohol.[218,219]
- Eliminating foods and beverages that are "irritating" to the patient. Chocolate,[220] peppermint,[221] onions and garlic,[222] have been reported to aggravate reflux symptoms.
- Decreasing or stopping smoking.[218,223]
- Eating small, non fatty meals (decreasing fat intake).[224]
- Remaining upright for at least 1 hour after meals.
- Avoiding straining or tight fitting garments.
- Relaxation training.[225]

Lifestyle modifications, particularly appropriate weight loss, are recommended as a part of therapy for all stages of disease.

This is a grade D recommendation.

4.3.2. Drug-Induced GERD

Some medications can decrease lower esophageal sphincter pressure thereby potentiating GERD in susceptible individuals. If possible, it may be wise to withhold these drugs in patients with GERD to see whether signs and symptoms improve.[190,191,226] Theophylline,[190] anticholinergic agents (e.g., tricyclic antidepressants),[226] nitrates, calcium channel blockers, especially nifedipine,[190,226] diazepam, alprazolam, and likely other benzodiazepines,[226-228] opiates including meperidine and morphine,[226] oral contraceptives,[190,226] and alendronate have been associated with GERD or esophagitis.[229]

4.3.3. Over-the-Counter (OTC) Medications

Patients suffering from GERD will often self-medicate using OTC products.[230,231] These include antacids, alginic acid, and low-dose H_2RAs. Antacids neutralize acid in the stomach and may increase lower esophageal sphincter pressure.[190,232] In patients with mild symptoms, they are effective in improving symptoms (frequency, severity, and duration) but do not promote esophageal healing in those patients with esophagitis.[233,234] Dosing these agents 7 times daily appears to be more effective than as needed or four times daily dosing.[234-238] Approximately 10-30% of patients obtain adequate symptom control on antacids alone.[239]

Most evidence exists for antacids containing aluminum or magnesium hydroxide. Aluminum-containing antacids are more likely to cause constipation whereas those containing magnesium more commonly cause diarrhea. Antacids may decrease the absorption of certain drugs including tetracycline, quinolone antibiotics (such as ciproflocaxin), ketoconazole, and itraconazole. In order to avoid risk of toxic accumulation of cations in patients with severe renal impairment (creatinine clearance <30ml/min), antacids should not be used for these patients.[240] Alginic acid is effective in relieving heartburn symptoms and may be superior to antacids[190,241-245] at least for meal-induced symptoms.[246,247] Low-dose H_2RAs are another self-medication alternative for patients with GERD.[248-252] Famotidine, ranitidine, and cimetidine are currently available over-the-counter. These agents are as effective as antacids in controlling heartburn.[231,253]

4.3 *Initial Therapy For GERD – Phase I*

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- Decreasing or stopping smoking.[218,223]
- Eating small, non fatty meals (decreasing fat intake).[224]
- Remaining upright for at least 1 hour after meals.
- Avoiding straining or tight fitting garments.
- Relaxation training.[225]

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This is a grade D recommendation.

4.3.2. *Drug-Induced GERD*

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Most evidence exists for antacids containing aluminum or magnesium hydroxide. Aluminum-containing antacids are more likely to cause constipation whereas those containing magnesium more commonly cause diarrhea. Antacids may decrease the absorption of certain drugs including tetracycline, quinolone antibiotics (such as ciprofloxacin), ketoconazole, and itraconazole. In order to avoid risk of toxic accumulation of cations in patients with severe renal impairment (creatinine clearance <30ml/min), antacids should not be used for these patients.[240] Alginic acid is effective in relieving heartburn symptoms and may be superior to antacids[190,241-245] at least for meal-induced symptoms.[246,247] Low-dose H_2RAs are another self-medication alternative for patients with GERD.[248-252] Famotidine, ranitidine, and cimetidine are currently available over-the-counter. These agents are as effective as antacids in controlling heartburn.[231,253]

Antacids, alginic acid, and low-dose H_2RAs can be recommended to improve mild heartburn or symptoms of reflux.[190,233,234,241,244,245] Patients who have frequent symptoms associated with meals may derive more benefit from using alginic acid compared to antacids alone.[246,247]

This is a grade B recommendation.

4.4 Initial Therapy For GERD – Phase II

Phase II therapy of GERD consists of prescription medications including full-dose H_2RAs or a PPI. Proton-pump inhibitors are superior to H_2RAs in GERD therapy but are more expensive than generic H_2RAs. Cisapride has been removed from the Canadian market because of serious cardiac events and should not be used (see Notes section below Table 5). Because GERD symptoms are so common, concern regarding the major expense of treating all GERD patients with PPIs from the onset of symptoms limits their widespread use.

The use of H_2RAs as first-line for patients with GERD symptoms is considered appropriate for mild to moderate symptoms. Mild symptoms are defined as: (a) symptoms occurring less than 3 times per week; (b) symptoms present for less than 6 months; (c) symptoms not interfering with daily activities; (d) pain (heartburn) intensity in symptoms of the order of 1-3 out of 10.[9] Severe symptoms are defined as: (a) daily attacks of reflux pain; (b) symptoms present for longer than 6 months; (c) symptoms regularly interfere with daily activities and can awaken patient at night; (d) pain (heartburn) intensity in symptoms of the order of 7 –10 out of 10.[9] Moderate symptoms are defined as mid-range between mild and severe[9] In reported clinical trials, symptomatic responses were seen in 28% of placebo users, 48% of H_2RA users, and 77% of PPI users over 12 weeks.[24,195,203] The corresponding healing rates for erosive esophagitis were 28%, 52% and 84% respectively for each drug class.[195,203,204]

Table 5 – Initial Therapy for GERD – Phase II

(Patients should be counselled about lifestyle modifications.)

Regimen	Evidence	4-Week Heartburn-Free Rate *	4-Week Healing Rate ‡	Drug Cost$	Comments
First Line Therapy					
H_2RA:					
Cimetidine 400mg bid x 4 weeks	[254-256]	36%	60%	$7.56	• *Agents of choice for patients with mild symptoms.[9] Symptom relief achieved in 36% of patients over 4 weeks and 45.2% over 8 weeks of therapy.[204]* • *If no response is seen after 4-8 weeks of therapy, a PPI may be used.[204,257]*
Famotidine 20mg bid x 4 weeks	[No RCT]	36%	60%	$35.36	
Nizatidine 150mg bid x 4 weeks	[No RCT]	36%	60%	$32.89	
Ranitidine 150mg bid x 4 weeks	[256,258-260]	36%	60%	$22.64	
PPI:					
Lansoprazole 30mg daily x 4 weeks	[17,262,262,270-274]	72%	82%	$56.00	• *Drugs of choice for patients with more severe reflux symptoms, or those with endoscopically documented erosive esophagitis, or those who do not respond to 4-8 weeks of H_2RA therapy.[9] Symptom relief achieved in 77% of patients over 8 weeks of PPI therapy.[204]*
Omeprazole 20mg daily x 4 weeks	[17,18,20,254,255,257, 259,259-261,267-272, 275-286]	72%	82%	$61.60	
Pantoprazole 40mg daily x 4 weeks	[18,20,274,285-291]	72%	82%	$53.20	

Notes:

- **Domperidone and metoclopramide:** not recommended because data do not support their use.
- **H_2RA:** H_2RAs are considered equally effective; cimetidine is the H_2RA of choice because of its low cost. The risk of central nervous system reactions (e.g., confusion, disorientation) is not higher with cimetidine compared to the other H_2RAs. If patient is taking theophylline, phenytoin, or warfarin along with cimetidine, monitor for toxicity of these agents (or consider using alternate H_2RA).
- **PPIs:** If no response after 4-8 weeks of PPI therapy, further work-up (as per algorithm) or referral to a specialist is likely necessary to rule out more serious conditions. PPIs are all considered to be safe and effective. Pantoprazole is the least expensive.
- **Cisapride:** withdrawn from market due to multiple contraindications and drug interactions resulting in serious cardiac events including death.[292-298]

RCT – Randomized Controlled Trial

$ - Approximate drug costs were derived from the ODB formulary and do not include professional fees or markups.

*– Symptom-free rates per class derived from reference.[204] Data extracted by drug class since too few studies exist to obtain data by individual drug.

‡- Healing rate based on one-armed meta-analysis of RCTs of patients with mild (Savary-Miller grade I-II) esophagitis conducted as part of this project. Data shown by drug class since too few studies exist to obtain data by individual drug.

The efficacy of H_2RAs and PPIs is well supported by RCTs for GERD therapy.
This is a Grade A recommendation.
Cost comparisons, in the absence of rigorous economic analyses, have led to recommendations to use H_2RAs initially, reserving PPIs for severe or resistant symptoms or disease. [209,299-301]

Antacids, alginic acid, and low-dose H_2RAs can be recommended to improve mild heartburn or symptoms of reflux.[140,233,234,241,244,245] Patients who have frequent symptoms associated with meals may derive more benefit from using alginic acid compared to antacids alone.[246,247]

This is a grade B recommendation.

4.4 Initial Therapy For GERD – Phase II

Phase II therapy of GERD consists of prescription medications including full-dose H_2RAs or a PPI. Proton-pump inhibitors are superior to H_2RAs in GERD therapy but are more expensive than generic H_2RAs. Cisapride has been removed from the Canadian market because of serious cardiac events and should not be used (see Notes section below Table 5). Because GERD symptoms are so common, concern regarding the major expense of treating all GERD patients with PPIs from the onset of symptoms limits their widespread use.

The use of H_2RAs as first-line for patients with GERD symptoms is considered appropriate for mild to moderate symptoms. Mild symptoms are defined as: (a) symptoms occurring less than 3 times per week; (b) symptoms present for less than 6 months; (c) symptoms not interfering with daily activities; (d) pain (heartburn) intensity in symptoms of the order of 1-3 out of 10.[v] Severe symptoms are defined as: (a) daily attacks of reflux pain; (b) symptoms present for longer than 6 months; (c) symptoms regularly interfere with daily activities and can awaken patient at night; (d) pain (heartburn) intensity in symptoms of the order of 7 –10 out of 10.[v] Moderate symptoms are defined as mid-range between mild and severe[v] In reported clinical trials, symptomatic responses were seen in 28% of placebo users, 48% of H_2RA users, and 77% of PPI users over 12 weeks.[24,195,203] The corresponding healing rates for erosive esophagitis were 28%, 52% and 84% respectively for each drug class.[195,203,204]

Table 5 – Initial Therapy for GERD – Phase II

(Patients should be counselled about lifestyle modifications.)

Regimen	Evidence	4-Week Heartburn-Free Rate *	4-Week Healing Rate ‡	Drug Cost$	Comments
First Line Therapy					
H_2RA:					
Cimetidine 400mg bid x 4 weeks	254-256	36%	60%	$7.56	• *Agents of choice for patients with mild symptoms.*[9] *Symptom relief achieved in 36% of patients over 4 weeks and 45.2% over 8 weeks of therapy.*[204] • *If no response is seen after 4-8 weeks of therapy, a PPI may be used.*[204,257]
Famotidine 20mg bid x 4 weeks	(No RCT)	36%	60%	$35.36	
Nizatidine 150mg bid x 4 weeks	(No RCT)	36%	60%	$32.89	
Ranitidine 150mg bid x 4 weeks	256,259,264-269	36%	60%	$22.64	
PPI:					
Lansoprazole 30mg daily x 4 weeks	17,262,262,270-274	72%	82%	$56.00	• *Drugs of choice for patients with more severe reflux symptoms, or those with endoscopically documented erosive esophagitis, or those who do not respond to 4-8 weeks of H_2RA therapy.*[9] *Symptom relief achieved in 77% of patients over 8 weeks of PPI therapy.*[204]
Omeprazole 20mg daily x 4 weeks	17,18,20,254,255,257, 259,259-261,267,272, 275-296	72%	82%	$61.60	
Pantoprazole 40mg daily x 4 weeks	18,20,274,285-291	72%	82%	$53.20	

Notes:

- **Domperidone and metoclopramide:** not recommended because data do not support their use.
- **H_2RA:** H_2RAs are considered equally effective; cimetidine is the H_2RA of choice because of its low cost. The risk of central nervous system reactions (e.g., confusion, disorientation) is not higher with cimetidine compared to the other H_2RAs. If patient is taking theophylline, phenytoin, or warfarin along with cimetidine, monitor for toxicity of these agents (or consider using alternate H_2RA).
- **PPIs:** If no response after 4-8 weeks of PPI therapy, further work-up (as per algorithm) or referral to a specialist is likely necessary to rule out more serious conditions. PPIs are all considered to be safe and effective. Pantoprazole is the least expensive.
- **Cisapride:** withdrawn from market due to multiple contraindications and drug interactions resulting in serious cardiac events including death.[292-298]

RCT – Randomized Controlled Trial

$ - Approximate drug costs were derived from the ODB formulary and do not include professional fees or markups.

*– Symptom-free rates per class derived from reference.[204] Data extracted by drug class since too few studies exist to obtain data by individual drug.

‡- Healing rate based on one-armed meta-analysis of RCTs of patients with mild (Savary-Miller grade I-II) esophagitis conducted as part of this project. Data shown by drug class since too few studies exist to obtain data by individual drug.

The efficacy of H_2RAs and PPIs is well supported by RCTs for GERD therapy.

This is a Grade A recommendation.

Cost comparisons, in the absence of rigorous economic analyses, have led to recommendations to use H_2RAs initially, reserving PPIs for severe or resistant symptoms or disease. [209,299-301]

4.5 Maintenance Therapy for GERD

Long-term maintenance therapy should be considered for patients with GERD in whom symptoms recur after the completion of an initial course of therapy.[9] A recent pooling of studies found the six-month relapse rate in the placebo arms to be 62% following successful treatment of grade II-IV esophagitis.[64,302-307] Many experts believe that serious underlying pathology (e.g., Barrett's esophagus) should be ruled out endoscopically before committing a patient to long-term acid suppression therapy (i.e., >6months).[2] Thus the concept of once-in-a-lifetime endoscopy has arisen.[2]

Effective maintenance therapy for GERD can be defined as treatment that keeps the patient's symptoms under control and prevents complications.[305] Some individuals will be controlled with antacids and lifestyle modifications alone. However, others will require prescription medications for adequate relief.[236,239] Some patients may eventually decide that they would prefer to undergo surgery rather than take medications chronically.[308,309] (See Section 4.6 - Refractory GERD)

All trials evaluating maintenance therapy are based on endoscopic outcomes and patients with erosive disease first healed using acid-suppression therapy. Trials based on symptoms alone are lacking. Anti-ulcer medicines are effective compared with placebo. Several RCTs have demonstrated that maintenance therapy with PPIs prevents GERD recurrences more effectively than continuous therapy with H_2RAs.[304,310-318] It is reasonable to continue maintenance therapy using the agent that was successful in relieving initial symptoms. Reducing the dose of medication or attempting maintenance with an agent less potent than was used for initial relief may result in recurrences.[310,313,319,320] A recent economic evaluation concluded that continuous or intermittent omeprazole therapy was more effective but more expensive than maintenance therapy with ranitidine or cisapride in patients with moderate to severe esophagitis.[64]

Table 6 – Maintenance Therapy for GERD

(Patients who receive maintenance therapy should be reminded about lifestyle modifications.)

Regimen	Evidence	Drug Cost $ (per 4 weeks)	Comments
First Line Therapy			
PPI:			
Lansoprazole 30mg daily	313,321-323	$56.00	• *Agents of choice in patients who required a PPI for initial relief or those who did not respond to H_2RAs.*[304,313,321,324,325]
Omeprazole 20mg daily	304,310,320,323,325-327	$61.60	
Pantoprazole 40mg daily	317,319,328,329	$53.20	
H_2RA:			
Cimetidine 400mg bid	(No RCT)	$7.56	• *Agents of choice in patients who obtained initial symptomatic relief on an H_2RA.*[324,325,330]
Famotidine 20mg bid	331	$35.36	
Nizatidine 150mg bid	(No RCT)	$32.89	
Ranitidine 150mg bid	310,320,321,325,326,330,332,333	$22.64	

Notes:

- Serious underlying pathology should be ruled out using endoscopy before committing the patient to long term acid suppression.
- Due to the intermittent nature of GERD, trials of therapy withdrawal are warranted.[*]
- **H_2RA:** Higher doses may be more effective but have not been tested in clinical trials. H_2RAs are considered equally effective; cimetidine is the H_2RA of choice because of its low cost. The risk of central nervous system reactions (e.g., confusion, disorientation) is not higher with cimetidine compared to the other H_2RAs. If patient is taking theophylline, phenytoin, or warfarin along with cimetidine, monitor for toxicity of these agents (or consider using alternate H_2RA).
- **PPIs:** Decreasing dose unlikely to be effective [319] Omeprazole 20mg daily is superior to 10mg daily.[304,334] Weekend dosing of PPI (i.e., 3 days/week) is not effective.[118] Giving a PPI intermittently for recurring episodes may be more cost-effective than maintenance therapy.[335,336] PPIs are all considered to be safe and effective. Pantoprazole is the least expensive.
- **Cisapride:** See Notes section below Table 5.[292,293,297]

RCT – Randomized Controlled Trial

$ Approximate drug costs were derived from the ODB formulary and do not include professional fees or markups.

H_2RAs and PPIs can be recommended for maintenance therapy for GERD. The choice of maintenance therapy should mirror the initial agent that successfully improved symptoms. PPIs are more effective for more severe, erosive disease.

This is a grade B recommendation.

Table 6 – Maintenance Therapy for GERD

(Patients who receive maintenance therapy should be reminded about lifestyle modifications.)

Regimen	Evidence	Drug Cost $ (per 4 weeks)	Comments
First Line Therapy			
PPI:			
Lansoprazole 30mg daily	[113,321,323]	$56.00	• *Agents of choice in patients who required a PPI for initial relief or those who did not respond to H_2RAs.*[304,313,321,324,325]
Omeprazole 20mg daily	[304,310,320,323,325,327]	$61.60	
Pantoprazole 40mg daily	[317,318,328,329]	$53.20	
H_2RA:			
Cimetidine 400mg bid	(No RCT)	$7.56	• *Agents of choice in patients who obtained initial symptomatic relief on an H_2RA.*[324,325,330]
Famotidine 20mg bid	[331]	$35.36	
Nizatidine 150mg bid	(No RCT)	$32.89	
Ranitidine 150mg bid	[310,320,321,325,326,330,332,333]	$22.64	

Notes:

- Serious underlying pathology should be ruled out using endoscopy before committing the patient to long term acid suppression.
- Due to the intermittent nature of GERD, trials of therapy withdrawal are warranted.[*]
- **H_2RA:** Higher doses may be more effective but have not been tested in clinical trials. H_2RAs are considered equally effective; cimetidine is the H_2RA of choice because of its low cost. The risk of central nervous system reactions (e.g., confusion, disorientation) is not higher with cimetidine compared to the other H_2RAs. If patient is taking theophylline, phenytoin, or warfarin along with cimetidine, monitor for toxicity of these agents (or consider using alternate H_2RA).
- **PPIs:** Decreasing dose unlikely to be effective.[319] Omeprazole 20mg daily is superior to 10mg daily.[318,334] Weekend dosing of PPI (i.e., 3 days/week) is not effective.[178] Giving a PPI intermittently for recurring episodes may be more cost-effective than maintenance therapy.[135,136] PPIs are all considered to be safe and effective. Pantoprazole is the least expensive.
- **Cisapride:** See Notes section below Table 5.[292,293,297]

RCT – Randomized Controlled Trial

$ Approximate drug costs were derived from the ODB formulary and do not include professional fees or markups.

H_2RAs and PPIs can be recommended for maintenance therapy for GERD. The choice of maintenance therapy should mirror the initial agent that successfully improved symptoms. PPIs are more effective for more severe, erosive disease.

This is a grade B recommendation.

4.6 Refractory GERD

Some patients will not respond to the treatments outlined above. Twenty-four hour ambulatory pH monitoring may be appropriate in order to document the duration and pattern of reflux episodes and to clarify its association with specific symptoms.[337] Further work-up by a specialist should also be considered at this point. Therapeutic options include the use of high dose PPIs as maintenance therapy, and anti-reflux surgery.[269,273]

Surgical techniques have evolved considerably in recent years. Laparoscopic anti-reflux surgery such as Nissen fundoplication or Toupet partial fundoplication are associated with less morbidity than the older open procedures.[195,308,309,338] There are however, only limited data on the long-term efficacy, cost, and sequelae of laparoscopic fundoplication. In addition, only one RCT compared maintenance drug therapy to surgery in order to assess their relative benefits and safety.[339] In this study, both measures were equivalent if patients in the omeprazole arm were allowed to titrate their dose.[339] Fundoplication will most often benefit individuals with the following characteristics: (I) low LES pressure (<6mm Hg); (ii) short overall LES length (2cm); or (iii) short intra-abdominal LES segment (<1cm).

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